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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,942	06/21/2001	Juha Punnonen	0179.210US	4876

30560 7590 02/25/2004

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	09/886,942	PUNNONEN, ET AL	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☒ Claim(s) *4 and 110* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/24/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: ATTACHMENTS 1 & 2

Continuation of Disposition of Claims: Claims pending in the application are 1,3,4,7,8,10-12,14-18,21-24,26-28,30-36,44-48,62-66,74-79,93,94,105-108 and 110-119.

Continuation of Disposition of Claims: Claims rejected are 1,3,7,8,10-12,14-18,21-24,26-28,30-36,44-48,62-66,74-79,93,94,105-108 and 111-119.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 12/01/2003, in which several claims were amended (claims 1, 7-8, 10, 17-18, 21-24, 26-28, 30-36, 74, 106, 108 and 118) and in which claims were cancelled (claims 2 and 109). Claims 1, 3-4, 7-8, 10-12, 14-18, 21-24, 26-28, 30-36, 44-48, 62-66, 74-79, 93-94, 105-108, 110-119 are pending in the instant application.

Response to Amendment

Applicants' amendment of several of the claims in the papers filed 12/01/2003 to read "at least 98% sequence identity to the polynucleotide sequence of SEQ ID NO: 8" has obviated the outstanding grounds of rejection under 35 U.S.C. 102 as being anticipated by Bebbington (WO 89/01036 A1). Similarly, the amendment of some of the claims to read "at least 99% sequence identity to the polynucleotide sequence of SEQ ID NO: 8" has obviated at least some of the outstanding grounds of rejection under 35 U.S.C. 102 as being anticipated by Chapman et al (Nucleic Acids Research, 1991, Vol. 19, No. 14, pages 3979-3986). However, several of the claims remain anticipated by the Chapman et al reference for reasons indicated below.

Several new grounds of rejection are made herein that were not necessitated by applicants' amendment of the claims in the papers filed 12/01/2003. Therefore, this action is not final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 8, 14-18, 105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Each of the rejected claims comprises a functional limitation wherein the level of promoter activity of the claimed nucleic acid is determined relative to two know CMV IE promoter sequences (i.e. the WT human AD169 and Towne CMV promoters, SEQ ID NOS: 19 & 20, respectively). The claims recite the limitations that the claimed nucleic acid promotes expression of an operably linked polypeptide-encoding nucleic acid "...at a level of expression that is about equal to or greater than..." the promoters described by SEQ ID NOS: 19 & 20. Alternatively, the level of promoter activity for the claimed nucleic acid is "...at a level that differs from..." that of the reference promoters. **This is a new rejection.**

Each of the rejected claims further recite the structural limitation that the claimed nucleic acid comprise a promoter sequence that is at least 98% identical to SEQ ID NO: 8 (1,767 nucleotides in length). If the promoter sequence is as large as that described by SEQ ID NO: 8, this encompasses approximately 16 nucleotide changes that can be made anywhere within SEQ ID NO: 8. Thus, rejected claims encompass a large genus of polynucleotide sequences that must retain the recited structural identity to SEQ ID NO: 8 as well as retaining the recited functional activity relative to that of the reference CMV promoters.

Applicants' specification is directed towards the "shuffling" methods for generating and identifying promoter sequences with desired properties (e.g. increased levels of promoter activity) where similar promoter sequences are randomly shuffled to produce novel sequences that are then screened for activity. For example, applicants used 4 different strains of CMV (human AD169 and Towne strains, monkey 68-1 and CSG strains) as a source for the template promoter sequences used in their "shuffling" protocol (e.g. Example 1, pages 60-61 of the instant specification). The specification teaches how to screen a library of such shuffled sequences to identify promoters having a desired level of activity (e.g. Figures 2-3). Applicants do demonstrate that SEQ ID NO: 8 has ~2-fold higher promoter activity than the reference sequences (see Figure 5, clone 6a8). As indicated by applicants' own data, a number of very different levels of activity can be generated within the shuffled library of promoters where the promoters have a relatively few number of changes between them (e.g. compare the activities of the clones in Figure 3 and Figure 5 with the corresponding sequences in Figure 8). The specification does not, however, provide a means for the skilled artisan to envision those specific embodiments comprising specific differences from SEQ ID NO: 8, for example, that will retain a particular level of activity relative to the reference promoters.

The prior art supports the contention that the addition or absence of specific nucleotide sequences within the CMV promoter can greatly alter functional activity. For example, Chapman et al teach that the presence of an ~400 nucleotide sequence 5' of the first intron of the CMV promoter can greatly reduce the level of expression such that it is "poor" relative to smaller nucleic acids lacking the upstream region (e.g. page 3982, column 2, last paragraph).

Given the large genus of nucleic acid sequences that must retain the very specific structural and functional characteristics of the rejected claims, the evidence from the prior art and applicants' specification that even small changes within the core CMV IE promoter region can have greatly differing effects on the level of promoter activity for the nucleic acids encompassed by the rejected claims, and given the lack of a means to envision *a priori* which particular sequences will meet the functional limitations of the claims, the skilled artisan would not have been able to envision a sufficient number of specific embodiments embraced by the claims to describe the broadly claimed genus of nucleic acids having the recited functional activity. Therefore, the skilled artisan would reasonably have concluded applicants were not in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 10-11, 21-24, 26-28, 30-36, 44-48, 62-66, 74-79, 93-94, 105 and 111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections.**

Claim 3 is vague and indefinite in that it is dependent upon a cancelled claim, claim 2. It would be remedial to amend the claim language to make claim 3 dependent upon claim 1.

Claim 111 is vague and indefinite in that it is dependent upon a cancelled claim, claim 109. It would be remedial to amend the claim language to make claim 111 dependent upon claim 108.

Claims 10, 21-24, 26-28, 30-36 each recite a limitation where the claimed nucleic acid comprises residues, substitutions or deletions "corresponding to about" specific residues of the consensus sequence shown in Figure 8 (i.e. SEQ ID NO: 21). These limitations are vague and indefinite in that it is unclear how many residues are encompassed by the term "corresponding to about". Does this term specify +/- three nucleotide residues? Ten nucleotide residues or a hundred residues? Secondly, the residues specifically recited in the claims do not correspond in number to those shown in Figure 8 (~1001-1770). Upon reading the specification, it appears that SEQ ID NO: 21 is intended to describe the consensus sequence shown in Figure 8. If this is accurate, it would be remedial to amend the claim to recite the appropriate residues of SEQ ID NO: 21.

Claim 36 is vague and indefinite in that the metes and bounds of the claim are unclear. It is unclear how a nucleic acid can have a deletion of approximately 193 nucleotides from within the middle of SEQ ID NO: 8 and retain the required 98% identity to SEQ ID NO: 8 (i.e. a change of ~190 nucleotides out of a total of 1,767 nucleotides is ~10% difference).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 12, 14-18, 24, 26-28, 35-36, 44-48, 62-66, 74-78, 105, 107 are rejected under 35 U.S.C. 102(b) as being anticipated by Chapman et al (Nucleic Acids Research, 1991, Vol. 19, No. 14, pages 3979-3986; see the entire document). **This rejection is maintained for reasons of record in Papers No. 16 & 20, mailed 12/6/02 and 7/30/2003, and repeated below.**

Chapman et al teach the construction and characterization of expression constructs comprising variations of a 2.4 kb fragment obtained for the hCMV Towne strain. The 2.4 kb hCMV sequence characterized by Chapman et al comprises total identity to SEQ ID NO: 8 of 95.8% and a local similarity of 98.8% over residues 335-2099 of the 2.4 kb sequence (e.g. see the attached search report). The fragments characterized by Chapman et al were demonstrated as driving expression of different coding sequences used as reporters for promoter activity (e.g. Tables I and II).

Various of the rejected claims comprise limitations where the claimed nucleic acid drives expression of a reporter sequence at different levels relative to expression of the same reporter from a given reference CMV promoter. Given the levels of expression for the different constructs characterized by Chapman et al, and given the high degree of identity to the constructs taught in the instant application, one of skill in the art would recognize that the constructs taught by Chapman et al would necessarily comprise the recited characteristics concerning expression levels in comparison to the reference CMV promoter. Similarly, one of skill in the art would recognize that the constructs of Chapman et al would express the encoding sequences well enough to induce an immune response in at least expression system.

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Response to Arguments

Applicant's arguments made in the response filed 12/1/2003 have been fully considered but they are not persuasive. The response essentially argues: 1) proof is required that the claimed invention necessarily possesses the limitations recited in the rejected claims (e.g. with regard to actual levels of expression as compared to SEQ ID NO: 19 or SEQ ID NO: 20), 2) the nucleic acid cited in the search report that is ~98% identical to SEQ ID NO: 8 comprises an additional ~400 nucleotides that is not present in the nucleic acids characterized by Chapman et al with regard to promoter activity and that the larger nucleic acid taught by Chapman et al (i.e. the subsequence that has 98% identity to SEQ ID NO: 8) would not "function properly" as a promoter because Chapman et al teaches that when the additional 400 nucleotides are present expression of a reporter sequence is "poor", 3) the smaller fragments taught by Chapman et al (i.e. ~461-2097 of SEQ ID NO: 8) are at best only about 91% identical to SEQ ID NO: 8, 4) Chapman et al teach that the additional 400 nucleotides are excluded since they relate to NF1 factors that have a negative effect on the expression of an operably linked reporter gene, and 5) Chapman et al do not teach an isolated or recombinant nucleic acid having at least 99% identity to SEQ ID NO: 8.

Applicants' amendment of the claims to delete the term "at least about 99%" sequence identity has obviated the grounds of rejection made above for embodiments that now read "at least 99%" sequence identity to SEQ ID NO: 8.

With regard to applicants' arguments concerning rejection of claims specifying a difference in promoter activity of the claimed nucleic acid as compared to reference promoters (i.e. SEQ ID NO: 19 and SEQ ID NO: 20), these arguments are not persuasive (e.g. claim 3). It is noted that the claims comprise the limitation "at a level that is about equal to or greater than". The term "about equal to" is not explicitly defined in the specification with regard to relative levels of gene expression and can be interpreted broadly to encompass a broad range of promoter activities. Second, as indicated in the rejection, the degree of sequence similarity between the Chapman et al sequence and SEQ ID NO: 8 is such that one of skill in the art would necessarily expect that the Chapman sequence would at least retain some promoter activity, which would be sufficient to meet the broad limitation of being "at a level of about equal to" that of the reference promoters. After all, applicants' own data shows that the promoter described by SEQ ID NO: 8 drives expression at least two-fold higher than the reference promoters (e.g. Figure 5, compare the results for clone 6a8 to the other two CMV IE promoters). Applicants' arguments concerning the ~400 nucleotides present in the larger sequence taught by Chapman et al mischaracterize the teachings of Chapman et al and imply that the larger sequence does not function at all as a promoter. The teaching by Chapman et al that "poor expression" was observed for the larger sequence comprising the additional ~400 nucleotides does not indicate that the promoter did not function at all. Again, given the limitation that the claimed promoter promotes expression of an operably-linked polypeptide encoding sequence "at a level that is

about equal to" that of the reference promoters, the larger nucleic acid taught by Chapman et al does in fact meet the minimal functional limitations of the rejected claims.

It is noted that the consensus sequence (i.e. SEQ ID NO: 21) is identical to SEQ ID NO: 8 over the residues specifically recited in the rejected claims (e.g. claim 35). As indicated on the attached search report, the sequence taught by Chapman et al comprises, for example, deletions of SEQ ID NO: 8 at residue 321). It is further noted that the term "corresponding to about" as applied to residues of the consensus sequence is not explicitly defined in the specification, such that the term can be interpreted to read broadly on any number of residues.

Claims 1, 3, 7-8, 12, 14-18, 44-48, 62-66, 74-79, 93-94, 106-108, 111-119 are rejected under 35 U.S.C. 102(e) as being anticipated by Haynes et al (U.S. Patent No. 6,200,959; see the entire patent).

The '959 patent teaches an approach to genetic vaccine methodology where a vector encoding an antigenic determinant of a filovirus is transfected into cells of the subject to be vaccinated so as to express the viral antigen in healthy cells to produce an immune response (e.g. Abstract). Haynes et al teach the construction and use of pWRG7077, a 4,326 bp expression vector, in their methodology for expressing a sequence encoding a viral antigen. Haynes et al teach that the vector comprises an HCMV IE promoter operatively linked to a multiple cloning site for insertion of antigen coding sequences (e.g. column 9, lines 7-24; SEQ ID NO: 7). Haynes et al demonstrate expression of operatively linked nucleic acid sequences encoding different glycoproteins derived from different filoviruses (e.g. columns 13-15). The attached

search report demonstrates that the promoter sequence from pWRG7077 has 99.1% sequence identity across nucleotides 123-1765 of SEQ ID NO: 8 of the instant invention.

Given the very high degree of identity between the sequence taught by the '959 patent and SEQ ID NO: 8, applicants' own data showing enhanced activity for SEQ ID NO: 8, and given the fact that Haynes et al demonstrate sufficient promoter activity for SEQ ID NO: 7 of their invention to generate an immune response in test animals (e.g. columns 15-16), it is reasonable to expect that the promoter taught by Haynes et al would have greater and/or different levels of promoter activity than the reference promoters described by SEQ ID NOS: 19 & 20. It is noted that some of the claims comprise the limitation "at a level that is about equal to or greater than". The term "about equal to" is not explicitly defined in the specification with regard to relative levels of gene expression and can be interpreted broadly to encompass a broad range of promoter activities. The degree of sequence similarity between the '959 sequence and SEQ ID NO: 8 is such that one of skill in the art would necessarily expect that the '959 sequence would at least retain some promoter activity, which would be sufficient to meet the broad limitation of being "at a level of about equal to" that of the reference promoters.

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 65-66 & 118-119 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. **This is a new rejection.**

Each of the claims is directed to a host cell transformed with a nucleic acid of the invention. The specification contemplates the use of the claimed nucleic acids for therapeutic purposes, including in human subjects. Therefore, the claims can be reasonably read to encompass a cell in a human and thus read on human beings. For these reasons, the claims are interpreted to read on nonstatutory subject matter.

Conclusion

No claims are allowed. Claims 4 and 110 are objected to as being dependent upon a rejected claim, but would be allowable if rewritten to include each of the limitations of the claims upon which they currently are dependent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER

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Art Unit 1636

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